Outer Retinal Morphology and Visual Function in Patients With Idiopathic Epiretinal Membrane

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Objective: To determine the relationship between the morphology of the fovea and visual acuity in patients with an untreated idiopathic epiretinal membrane (ERM).

Methods: We examined 52 eyes of 45 patients diagnosed with an ERM. The morphology of the foveal area was determined by spectral-domain optical coherence tomography. The relationships between the best-corrected visual acuity (BCVA) and 8 optical coherence tomography features, central retinal thickness, cone outer segment tip (COST) line, photoreceptor inner/outer segment (IS/OS) junction line, foveal bulge of the IS/OS line, external limiting membrane, inner limiting membrane, foveal pit, and ERM over the foveal center, were evaluated.

Results: Multiple regression analysis showed that intact COST line, IS/OS junction line, and external limiting membrane independently and significantly contributed to the BCVA. The standardized partial regression coefficient $\beta$ was 0.415 for the COST line, 0.287 for the IS/OS junction line, and 0.247 for the external limiting membrane. However, the other features, eg, foveal bulge, inner limiting membrane, foveal pit, and ERM, were not significantly associated with the BCVA. The central retinal thickness was significantly correlated with the BCVA ($r^2=0.274; P<.01$).

Conclusions: At an early stage of an ERM, only the photoreceptor structures are significantly associated with the BCVA, and the appearance of the COST line was most highly associated. Detailed examinations of the photoreceptor structures using optical coherence tomography may help find photoreceptor dysfunction in cases of idiopathic ERM.


OPTICAL COHERENCE TOMOGRAPHY (OCT) is a useful method of detecting early morphological changes in retinas affected by various pathological conditions. The correlations between the visual acuity and the morphological changes in the retina have been reported for various retinal diseases, such as age-related macular degeneration, central serous chorioretinopathy, macular edema, idiopathic macular hole, and epiretinal membrane (ERM).

Retinal traction caused by an ERM leads to morphological changes of not only the superficial layers of the retina but also the entire retina including the photoreceptor layer. This is important because long-standing morphological changes can lead to functional damages and cause metamorphopsia and decreased visual acuity.

Spectral-domain OCT (SD-OCT) has enabled clinicians and investigators to obtain clearer images of the microstructure of the photoreceptor layer than time-domain OCT. Several studies have examined whether significant correlations exist between macular dysfunction and the integrity of photoreceptor microstructures, especially the photoreceptor inner segment/outer segment (IS/OS) junction line, detected by SD-OCT in patients with an ERM.

The diagnostic value of determining the integrity of the IS/OS junction line and the cone outer segment tip (COST) line by SD-OCT has been done primarily on diseases of the outer retina, eg, acute zonal occult outer retinopathy and hereditary macular dystrophies. However, in eyes with an ERM, the appearance of the photoreceptor microstructures in the SD-OCT image can be affected by retinal thickening, subretinal cysts, and the ERM itself. These alterations lead to a reduction in the intensity of the laser light reaching the photoreceptor layer. In addition, the clarity of the SD-OCT images of the outer retina, eg, the Henle layer, IS/OS junction line, and COST line, is dependent on the incidence angle of the laser beam on the retina, which would be altered by an ERM.

Thus, the diagnostic value of examining the photoreceptor microstructures by SD-OCT in eyes with an ERM may not be as reliable as in cases of acute zonal occult outer retinopathy and other outer retinal diseases where the inner retinal alterations do not attenuate the laser energy.

The purpose of this study was to evaluate the relationship between deteriora-
tion of the best-corrected visual acuity (BCVA) and abnormalities of the photoreceptor microstructures in patients with untreated idiopathic ERM. To accomplish this, we examined cases with ERM without severely deformed inner structures, such as a lamellar hole and large cystic formations. We classified the abnormalities of the retina in the SD-OCT images and performed multiple regression analyses to determine which parameter was independently and significantly associated with the BCVA in cases of ERM.

METHODS

This was a retrospective case series performed in the Department of Ophthalmology, National Tokyo Medical Center, Tokyo, Japan. After an explanation of the procedures to be used, an informed consent was received from all of the subjects for the tests. The procedures used adhered to the tenets of the Declaration of Helsinki, and approval to perform this study was obtained from the review board/ethics committee of the Tokyo Medical Center.

We examined 52 eyes of 45 patients (20 eyes of 18 men and 32 eyes of 27 women; mean [SD] age, 67.0 [10.0] years) diagnosed with an ERM without lamellar holes or apparent cystic changes in the fovea. The patients were examined between October 2009 and September 2010. The exclusion criteria were myopia more than 8 diopters, advanced lens opacification, other ocular disease that could cause visual disturbances, secondary ERM caused by vascular diseases, uveitis, and retinal detachment. Cases whose OCT images did not have enough signal intensity for evaluation, ie, average intensity of the SD-OCT signal was less than 8 of 10, were also excluded.

Spectral-domain OCT (Cirrus HD-OCT, versions 4.5 and 5.1; Carl Zeiss Meditec) was used to obtain tomographic images of the retina. Following dilation of the pupil, 5 line-scan images were obtained both horizontally (length, 9.0 mm) and vertically (length, 6.0 mm) across the fovea, with the distance between each scan line of 0.075 mm. Cases where any of the scan lines did not pass through the ERM were excluded. Eight SD-OCT features were evaluated: (1) central retinal thickness (CRT), (2) COST line, (3) IS/OS junction line, (4) bulgelike appearance of the IS/OS junction line at the foveola (foveal bulge), (5) external limiting membrane (ELM), (6) internal limiting membrane (ILM), (7) foveal pit, and (8) ERM formation over the foveal center.

The CRT was defined as the distance between the inner retinal surface and inner surface of the retinal pigment epithelium at the foveola (Figure 1A). It was measured manually by the built-in scale of the SD-OCT system.

The microstructures within a 500-μm diameter of the fovea (Figure 1A, scale bar) were graded independently by 2 experienced ophthalmologists (K.W. and K.T.) (Table 1) to be either normal or abnormal. During this procedure, all of the patients’ information, including the BCVA, was masked to the examiners. In cases where the gradings were different, discussions were held until both examiners agreed. In earlier studies, the OCT features were graded into 3 classes, eg, normal ILM, mild ILM distortion, and severe ILM distortion.9,17 We initially adopted a similar classification; however, we found it confusing especially in distinguishing mildly from severely abnormal structures. We have thus simplified the classification to normal or abnormal.

The COST line, IS/OS junction line, and ELM were graded normal when they were seen clearly and appeared continuous in the foveal region, and they were graded abnormal when they were blurred, interrupted, or absent. The foveal bulge is an elevation of the IS/OS junction line that appears like a dome over the foveola. We graded it normal when the bulgelike appearance was clearly observed and graded it abnormal when the bulgelike appearance was not observed and the IS/OS junction line appeared flat.

The ILM was graded normal when it looked smooth and flat at the fovea and was graded abnormal when it looked wrinkled or distorted. The foveal pit was graded normal when the concave retinal surface was clearly observed at the foveola and graded abnormal when the foveal surface appeared flat. The ERM was graded normal when the ERM did not overlap the foveola and graded abnormal when the ERM was attached over the foveola.

The relationship between these 8 OCT features and the visual acuity was statistically examined. Statistical analysis was performed using SPSS version 19.0 (SPSS Japan). The visual acuity was converted to logMAR units for the statistical analyses. Pearson correlations were performed to determine the association between CRT and visual acuity. The Mann-Whitney test was used to compare the BCVA and CRT between the normal and abnormal groups for each OCT feature. Multiple regression analysis was performed with BCVA and CRT as the dependent variables and with the integrities of 7 OCT features as independent variables. A P value <.05 was considered significant.

RESULTS

We first evaluated the normal fellow eyes of 29 of the 45 patients studied (13 eyes of 13 men and 16 eyes of 16 women; mean [SD] age, 66.0 [8.1] years). For these, all of the 7 OCT features were judged normal.18 Two representative cases demonstrating how the OCT features were judged to be either normal or abnormal are shown in Figure 1B and C. A horizontal SD-OCT scan image of the left retina of a 74-year-old man is shown in Figure 1B. The ELM, foveal bulge, IS/OS junction line, and COST line were clearly observed and judged to be normal. An ERM was present over the foveola, and this was judged to be abnormal. The foveal pit was concave and judged to be normal. The ILM was partially wrinkled at the foveola and judged abnormal.

A vertical SD-OCT scan image of the right retina of a 65-year-old woman is shown in Figure 1C. The IS/OS junction line and ELM were clearly observed and judged to be normal. The foveal bulge and COST line could not be seen at the fovea and were judged abnormal. The ILM was wrinkled in the parafoveal region; however, the foveal region within 500 μm of the foveola was spared and judged normal. The foveal pit was judged abnormal because the foveola was elevated by a tangential traction from the ERM and the foveal pit was flattened. An ERM covered the foveola and was judged abnormal.

The BCVA and CRT of the normal eyes were compared with those of the abnormal groups for each OCT feature of the 52 cases by Mann-Whitney test (Figure 2). The BCVA was significantly better in cases when 6 OCT features were judged to be normal: COST line, IS/OS junction line, foveal bulge, ELM, foveal pit, and ERM (Figure 2A). The CRT was significantly thinner in cases when 5 OCT features were judged to be normal: COST line, IS/OS junction line, foveal bulge, foveal pit, and ERM (Figure 2B).

Subsequently, multiple regression analyses were performed to determine the independent predictors of the BCVA and CRT in eyes with an ERM. The analyses showed...
Figure 1. Optical coherence tomography images. A, Horizontal optical coherence tomography image of the retina of a normal eye with a magnified image showing the locations of the external limiting membrane (ELM), photoreceptor inner segment/outer segment junction line (IS/OS), cone outer segment tip line (COST), retinal pigment epithelium (RPE), foveal bulge (asterisk), and central retinal thickness (CRT) (arrow). Scale bar=500 µm. B and C, Classification of 7 features in spectral-domain optical coherence tomography image in patients with an epiretinal membrane (ERM). A indicates abnormal; ILM, internal limiting membrane; and N, normal.
that the predictive variables for BCVA were COST line \( (P < .001) \), IS/OS junction line \( (P = .02) \), and ELM \( (P = .03) \). The standardized partial regression coefficient \( \beta \) was 0.415 for the COST line, 0.287 for the IS/OS junction line, and 0.247 for the ELM (Table 2). On the other hand, the predictive variables for the CRT were foveal pit \( (P < .001) \), ERM \( (P = .003) \), and foveal bulge \( (P = .04) \). The standardized partial regression coefficient \( \beta \) was 0.476 for the foveal pit, 0.337 for the ERM, and 0.182 for the foveal bulge (Table 3).

The CRT was measured at the foveal center in 52 cases, and a significantly positive correlation was observed between the CRT and the BCVA \( (r^2 = 0.274; P < .01) \) (Figure 3).

**COMMENT**

The relationships between the outer retinal microstructures determined by SD-OCT and the BCVA have been reported previously for patients with ERM.\(^7-10\) The de-

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**Table 1. Classification of OCT Features in the Foveal Region**

<table>
<thead>
<tr>
<th>Classification</th>
<th>COST</th>
<th>IS/OS</th>
<th>Foveal Bulge</th>
<th>ELM</th>
<th>ILM</th>
<th>Foveal Pit</th>
<th>ERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear and continuous</td>
<td>Clear and continuous</td>
<td>Observed</td>
<td>Clear and continuous</td>
<td>Smooth and flat</td>
<td>Observed</td>
<td>Foveola is free of ERM</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Blurred, interrupted, or absent</td>
<td>Blurred, interrupted, or absent</td>
<td>Not observed</td>
<td>Blurred, interrupted, or absent</td>
<td>Wrinkled or distorted</td>
<td>Not observed</td>
<td>ERM is attached over foveola</td>
</tr>
</tbody>
</table>

Abbreviations: COST, cone outer segment tip line; ELM, external limiting membrane; ERM, epiretinal membrane; ILM, internal limiting membrane; IS/OS, photoreceptor inner segment/outer segment junction line; OCT, optical coherence tomography.
sign of our study was different from these earlier studies because we evaluated the OCT features only in the foveal region within 500 µm of the center because the visual acuity is mainly determined by the foveal center. In addition, we excluded patients who had small lamellar holes or apparent cystic changes in the fovea, which can induce optical artifacts and distort the appearances of the photoreceptor layer in the OCT images.

Multiple regression analyses showed that the integrity of the COST line was most strongly associated with the BCVA, followed by the IS/OS junction line and the ELM. On the other hand, the foveal bulge, ILM, foveal pit, and ERM were not significantly associated with the BCVA. It has been reported that the integrity of the IS/OS junction line is significantly associated with the postoperative BCVA.7,8 Our results showed that not only the IS/OS junction but also the COST line were most strongly associated with the postoperative BCVA (β = 0.415 for COST line; β = 0.287 for IS/OS junction). Abnormalities of the COST line have been suggested to be an early sign of photoreceptor dysfunction in eyes with outer retinal disorders.11,19 In cases of ERM, the appearance of the COST line at the fovea should be carefully examined to determine if early changes in retinal function might be present.

In patients with an ERM, the retinal thickening could affect the appearance of the images of the photoreceptor layer. Multiple regression analysis showed that abnormalities in the COST line, IS/OS junction line, and ELM were not significantly associated with the CRT (Table 2 and Table 3), although an absence of the foveal pit (P < .001) and existence of foveal ERM over the foveola (P = .003) were independently associated with the CRT. These results suggest that the photoreceptor microstructures appeared abnormal not because of the reduced laser light through thickened retina but because of real morphological changes. The abnormality in the inner retinal structures, eg, ILM, foveal pit, and ERM at the foveola, might affect the visual acuity because they would alter the optical characteristics of the retina. However, the results of multiple regression analysis showed that these inner retinal abnormalities did not significantly contribute to the BCVA at least in the early stage of ERM.

The correlations between the 4 highly refractive bands in the outer retina seen in the SD-OCT images and the retinal histologic features have been well investigated.16,20,21 There has been an early consensus on the interpretation of the first and fourth bands in the outer retina, the innermost band representing the ELM and the outermost band representing the complex of the retinal pigment epithelium and Bruch membrane. The second band was initially thought to arise from the differences in the refractive index between the inner and outer segments of the photoreceptor and thus called the photoreceptor IS/OS junction line. However, Fernández et al21 found it to represent the ellipsoids of the photoreceptor inner segment by ultra-high-resolution OCT with adaptive optics. The third band has been found to represent the junction between the cone outer segment and the apical microvilli of the retinal pigment epithelium and is called the COST line.16,21 The ellipsoids in the photoreceptor inner segments are rich in mitochondria and crucial for the metabolism of the photoreceptors. The cone outer segments contain the photopigment discs, which are also important for phototransduction. The strong contributions of the COST and IS/OS junction lines to the BCVA but not to the CRT suggest that both the microstructure and function of the photoreceptors were damaged by the ERM.

The OCT abnormalities in the photoreceptor microstructures have been reported to be significantly correlated with the loss of visual acuity and visual field in acute zonal occult outer retinopathy and retinal dystrophies where the photoreceptors are primarily affected.11,16 On the other hand, the abnormal ERM develops on the surface of the retina without directly affecting the photoreceptor layer. The membrane can then cause tangential traction over the macula, followed by an inward traction toward the vitreous cavity at the foveal pit. Long-standing inward traction may cause formations of cysts in the outer nuclear layer.

Table 2. Multiple Regression Analyses to Determine the Independent Predictors of the Best-Corrected Visual Acuity

<table>
<thead>
<tr>
<th>Standardized Partial Regression Coefficient (β)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>0.415</td>
</tr>
<tr>
<td>IS/OS</td>
<td>0.287</td>
</tr>
<tr>
<td>ELM</td>
<td>0.247</td>
</tr>
</tbody>
</table>

Abbreviations: COST, cone outer segment tip line; ELM, external limiting membrane; IS/OS, photoreceptor inner segment/outer segment junction line.

Table 3. Multiple Regression Analyses to Determine the Independent Predictors of the Central Retinal Thickness

<table>
<thead>
<tr>
<th>Standardized Partial Regression Coefficient (β)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal pit</td>
<td>0.476</td>
</tr>
<tr>
<td>ERM</td>
<td>0.337</td>
</tr>
<tr>
<td>Foveal bulge</td>
<td>0.182</td>
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</table>

Abbreviation: ERM, epiretinal membrane.

Figure 3. Significant correlation between central retinal thickness (CRT) and best-corrected visual acuity (BCVA) in 52 eyes. Pearson correlation coefficient r² was 0.274 (P < .01).
and microstructural changes in the photoreceptor.\textsuperscript{7,8,22,23} Thus, the etiology of the OCT abnormalities of the photoreceptor layer observed in eyes with an ERM should be different from that of outer retinal diseases.

Niwa et al\textsuperscript{14} measured focal macular electroretinograms (fmERGs) elicited by 15\textsuperscript{3}t stimuli in 37 patients with an ERM and concluded that the inner retinal layer was predominantly impaired initially and that the visual dysfunction in eyes with ERM may have resulted from macular edema. They also found that the correlation between the visual acuity and the degree of amplitude reduction of the a, b wave, and oscillatory potentials was not significant. However, they reported that the visual acuity largely depended on a very limited region of the fovea, and the stimulated region of 15\textsuperscript{3}t stimuli did not necessarily exclude the fact that the photoreceptor function was primarily affected by the ERM. Considering that mechanical traction is extraordinarily severe in the foveola as shown in Figure 1B and C, and the outer nuclear layer within 500 \textmu m of the foveola is thicker than in the parafoveal region. Thus, the results of fmERGs elicited by 15\textsuperscript{3}t stimuli did not necessarily exclude the fact that the photoreceptor function was primarily affected by the ERM. Considering that mechanical traction is extraordinarily severe in the foveola, the photoreceptor function may be primarily impaired even at the early stage of ERM, leading to the reduction of the BCVA.

There are reports that the reduction in the visual acuity in eyes with an ERM is due to retinal thickening,\textsuperscript{7,10} and our results also indicated that the thickness of the outer retina, ie, combined thickness of outer nuclear layer and photoreceptor layer, was correlated with visual acuity (Figure 3). Together with the results of multiple regression analysis, functional damage of the photoreceptor due to long-standing inward traction was determined to be a strong contributor to the visual acuity reduction. Thus, detailed examinations of the photoreceptor microstructures in the OCT images may help find early visual dysfunction in cases of idiopathic ERM.

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